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How not to conduct a clinical trial

Research suspended at Oklahoma campus after numerous flaws

By Edward T. Pound, USA TODAY

WASHINGTON - In March 1997, a leading physician at the University of Oklahoma's College of Medicine in Tulsa got the go-ahead to test an experimental vaccine on patients with advanced melanoma, a skin cancer that can kill. But, federal health officials say, Michael McGee's experiment repeatedly violated safety standards and represents a case study in how not to conduct a clinical trial.

The university quietly shut down the trial three months ago after an outside clinical research firm issued two evaluation reports sharply critical of McGee. The firm said he withheld information from patients when his study went awry.

On June 29, the Department of Health and Human Services (HHS) shut down all government-sponsored clinical research at the Tulsa campus, which includes five studies and about $700,000 in indirect funding. The university itself suspended 70 other non-government research projects until it can determine that all federal safety regulations are being followed, according to university officials.

University officials say 26 of 98 patients in the vaccine trial have died, but they emphasize that there is no indication that the vaccine had caused the deaths. A preliminary review of "serious adverse event" reports indicated that they had succumbed to the "progression of the disease," an official says.

University administrators say they disbanded the Institutional Review Board, or IRB, at Tulsa, which was responsible for monitoring the safety of patients in McGee's and other trials. They also took swift personnel actions. Last Monday, the IRB chairman, Daniel Plunket, was removed from his position as senior associate dean for clinical affairs at the College of Medicine, according to university administrators. McGee, they say, was removed as vice chairman of the Department of Surgery. Edward Wortham Jr., the director of the Office of Research at the Health Sciences Center, was relieved of his administrative duties.

"We are very concerned. That is why we stopped all the research we are doing in Tulsa," says Ken Lackey, president of the Tulsa campus. Lackey was named to a universitywide task force created by David Boren, the university's president, to review compliance procedures in trials.

McGee declined to comment. Lackey says McGee's "intentions were completely honorable," though "it may be his activities and methods did not meet the standards set by the government and the university."

In a brief telephone interview, Plunket said: "It is a very complex issue. It is being thoroughly reviewed as we speak. It will all come out in the wash." Wortham did not respond to a telephone call or an e-mail seeking comment.

The suspension of the Tulsa campus's government-sponsored research programs was ordered by Michael Carome, the chief compliance official in the new HHS Office for Human Research Protections. That office was recently created as part of HHS' efforts to step up enforcement against universities, hospitals and others that fail to follow regulations meant to protect human subjects.

In the past 20 months, HHS has taken disciplinary action against several major institutions. In addition, HHS Inspector General June Gibbs Brown has issued several critical reports on the failure of the government, researchers and Institutional Review Boards to protect subjects in clinical trials.

In the Tulsa case, McGee and the College of Medicine acted as sponsors of the study. He was the principal investigator and developed a vaccine for the study. The vaccine was injected in 94 patients who were ill with melanoma.

McGee did not explain the study clearly to his patients, according to a letter Carome wrote June 29 announcing the suspension. Carome wrote that the idea was to determine the side effects and toxicity of the vaccine and to assess the response of patients' immune systems. But, he said, McGee did not explain that to patients enrolled in his three-year study, which was conducted at the university in Tulsa and at eight other sites. Carome said McGee's description was "inadequate."

The study began to unravel in January. University officials did not report the problems with the cancer trial to HHS officials, though researchers did inform the Food and Drug Administration of "minor" problems this past January.

Carome laid out his agency's findings in his letter June 29:

In March, an outside research company, Hausmann & Wynne Associates, urged that the trial be halted to protect patients.

In their reports, Hausmann & Wynne said McGee and other university personnel were not experienced enough to be conducting the trial: "The background and understanding of the personnel conducting the study is considered to be inadequate to assure the safety of study patients."

McGee and the College of Medicine made the vaccine, but "manufacturing facilities were inadequate," Hausmann & Wynne wrote.

Hausmann & Wynne said the melanoma vaccine should be "quarantined" to prevent accidental use and destroyed or marked "Not for use in humans."

On April 10, McGee wrote surviving subjects and investigators at other sites that he was stopping injections because he didn't have adequate supplies of the vaccine. About a week later, the chairman of the Tulsa IRB, Plunket, informed other IRB members that the melanoma trial had been put on hold because "Dr. McGee and his co-workers have found some problems with vaccine production and data keeping."

Carome said McGee and Plunket had "misrepresented the reasons for the suspension and minimized the seriousness of the findings" in the Hausmann & Wynne evaluations.

McGee made substantial changes to the study without receiving the required IRB approval. In one case, the vaccine was shipped to some subjects' homes for self-injection. The IRB-approved protocol for the study required that researchers give all injections.

The IRB itself came in for heavy criticism. Carome's staff said the internal watchdog "failed to conduct substantive and meaningful continuing review."